REMARKS

The Office Action of September 19, 2008, has been carefully studied. Claims 8-11, 16-18, 25-28 and 35 currently appear in this application. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicant respectfully requests favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

Claim Amendments

Claim 27 has been amended further to define Crystal Form E. Support for this amendment can be found in the specification as filed at page 7, lines 19-21.

Art Rejections

Claims 28 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Miura, US 5,959,088. The Examiner alleges that Miura discloses the claimed Form D crystals of a

hemifumarate of a compound of Formula I and asserts that preparation of **an old compound** [emphasis added] by a different method does not result in a patentably distinct compound.

This rejection is respectfully traversed. Both claims 28 and 35 claim Crystal Form D of a hemifumarate hydrate of a compound of formula (I), **which crystal is obtained from Crystal Form E**. The Crystal Form D prepared from Crystal Form E possesses superior properties, including reduced content of residual solvent and a larger particle size. These properties are recited in the specification of Hiraide et al., U.S. Application No. 10/399,126, Published Application 2003/0191296, a copy of which is submitted herewith. It can be seen from Hiraide that the Crystal Form D prepared from Crystal Form E as claimed herein is different from the Crystal Form D of Miura in content of residual solvent and particle size. In other words, Crystal Form D as claimed herein is a new substance. Therefore, it is respectfully submitted that the

Examiner's assertion that a compound of formula (I) as claimed in claims 28 and 35 is an old compound is groundless and improper.

Furthermore, the Examiner insists that Miura discloses the claimed Form D crystals of hemifumarte hydrate of a compound of formula (I) in Figures 7 and 8. However, it is respectfully submitted that Miura Figures 7 and 8 do not show the herein clamed compound.

Figures 7 and 8 of Miura on show the results of stability testing with Crystal Forms A, C, and D, more specifically, a change in the percent retentions of Crystal Forms A, C and D. It is respectfully submitted that these figures cannot be said to disclose the compound claimed herein. In addition, as discussed above, both claims 28 and 35 claim Crystal Form D of a hemifumarate hydrate of a compound of Formula I **which crystal is obtained via Crystal Form E**. The Crystal Form D claimed herein differs from the Crystal Form D of Miura in content of residual solvent and particle size, both of which

differences would not be expected merely because the preparation of the two compounds is different.

In Hiraide, it is noted at paragraph 0010 that prior art D-type crystals prepared by conventionally known techniques have a number of problems, including a large volume of crystallization solvent remaining in the crystal as a residual solvent; the residual solvent is difficult to remove during drying, and the dryness of the residual solvent cannot be below 1500 ppm. The prior art D-type crystal also involves another problem of having a small particle size, which makes it difficult to prepare tablets comprising this crystal.

It is well established patent law that in order to find anticipation, each element of a claim must be contained in one reference. In other words, "…anticipation under section 102 can be found only when the reference discloses exactly what is claimed." *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 708; 227 USPQ 773, 777 (Fed. Cir. 1985). In

the present case, there is nothing in Miura that discloses the particular Crystal Form D claimed herein, as the method of making the Crystal Form D claimed herein is different from that of Miura and provides unexpectedly superior properties of the claimed compound.

Claims 8-11, 25-28 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miura in view of Spanton et al., US 5,945,405.

This rejection is respectfully traversed.

The Examiner points out, "in paragraph [0071] of the specification it is stated that crystal Forms G are solvates of Crystal Form D." However, paragraph [0071] heads as follows:

> Iso-structural solvate G-form crystals, namely, Crystal form G1, Crystal form G2 and Crystal form G3 of the present invention can be obtained by directly or indirectly contacting hydrate Crystal form D described below with a specific solvent as described below.

It is respectfully submitted that Crystal Forms G are not merely solvates of Crystal Form D.

As has been previously discussed, Crystal Forms G are novel crystal forms which are different from Crystal Form D. This is clear from Figures 2, 3, 5, 6 and 7 of the present application. Therefore, it is respectfully submitted that the Examiner's allegation that the crystal forms are solvates of known crystal forms is groundless and improper.

As described in the present specification, Crystal Form G can be obtained by contacting Crystal Form D hydrate with a specific solvent. However, Miura neither explains nor describes the Crystal Form D hydrates as a starting material. Accordingly, it is respectfully submitted that the Examiner's assertion is based on hindsight.

Spanton adds nothing to Miura, as Spanton merely discloses tetrahydrofuran solvates of erythromycin derivatives. There is nothing in

Spanton that suggests the Crystal Forms claimed herein.

Claims 16-18, 23, 25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miura in view of Spanton and further in view of Bosch et al., US 6,504,017.

This rejection is respectfully traversed. As noted above, since Crystal Forms G are not obvious over Miura, one skilled in the art would not obtain Crystal Form D hydrate using one of the Crystal Forms G as a starting material. Again, it is respectfully submitted that the Examiner's rejection is based upon hindsight.

The process recited in claim 18 comprises the step of conditioning Crystal Form D anhydrate to obtain Crystal Form D hydrate. The Crystal Form D hydrate thus obtained possesses superior properties as a pharmaceutical material. In contrast thereto, none of Miura, Spanton or Bosch discloses or suggests the conditioning step for obtaining the specific crystal from of Crystal Form D hydrate.

Accordingly, it is respectfully submitted that the combination of Miura, Spanton and Bosch does not render the present claims obvious.

In response to applicant's assertion that the prior art of record does not disclose the process of claim 27, the Examiner insists that this argument has not been found persuasive since Crystal Form E has not been defined in claim 27. It should be noted that claim 27 has been amended better to define Crystal form E. None of Miura, Spanton or Bosch discloses or suggests that Crystal Form E, nor does any one of these cited references disclose or suggest that Crystal Form D having a reduced content of residual solvent and a larger particle size than previously obtained can be produced by **preparing it via Crystal form E** Accordingly, it is respectfully submitted that the process of claim 27 is not obvious over the combination of Miura, Spanton or Bosch.

Claim 25, like claim 27, relates to a process for preparing Crystal Form D anhydrate via Crystal Form E. In addition, Crystal Form D anhydrate is useful as an intermediate to produce Crystal Form D hydrate. Accordingly, it is respectfully submitted that claim 25 is not obvious over the combination of Miura, Spanton and Bosch.

The Examiner asserts, "Further, note that Crystal form E would be expected to lose its crystalline structure when dissolved in water and result in an erythromycin derivative disclosed by the prior art of record." The claims are not drawn to a solution of Crystal Form E, and the Examiner is invited to explain the scientific ground on which Crystal Form E would be expected to lose its crystalline structure. In this case, it is respectfully submitted that the burden of proof is on the Examiner.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

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(54) ERYTHROMYCIN DERIVATIVE HAVING NOVEL CRYSTAL STRUCTURES AND PROCESSES FOR THEIR PRODUCTION

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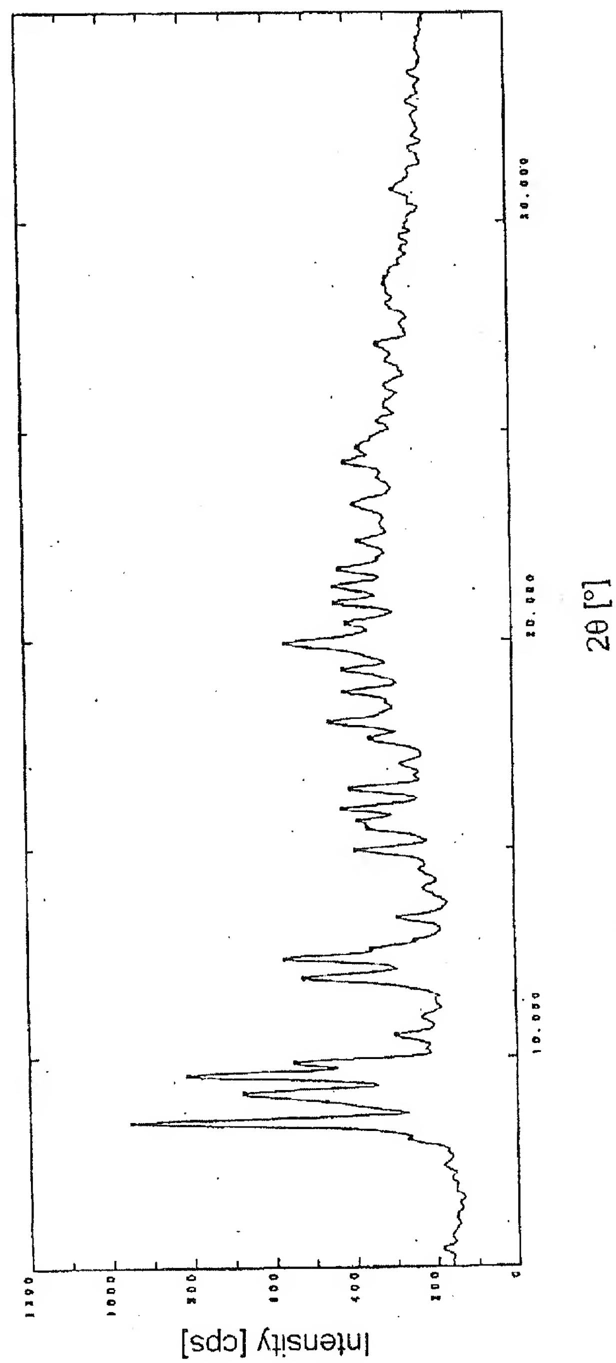
(57) ABSTRACT

The present invention provides an E-type crystal of N-demethyl-N-isopropyl-12-methoxy-11-oxo-8,9-anhydroerythromycin A-6,9-hemiacetal fumarate having strong diffraction peaks at diffraction angles (2θ) of 5.6° and 10.4° as measured by powder X-ray diffractometry, which is prepared by treating a C-type crystal of the compound in a mixed solvent of ethyl acetate and water at 20° C. to 40° C., and a D-type crystal prepared via the E-type crystal. These crystals have a reduced content of residual solvent and high suitability for formulation.

Fig. 1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2θ [°]
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1000
800
600
400
200
0
10.000
20.000
30.000

Fig. 2

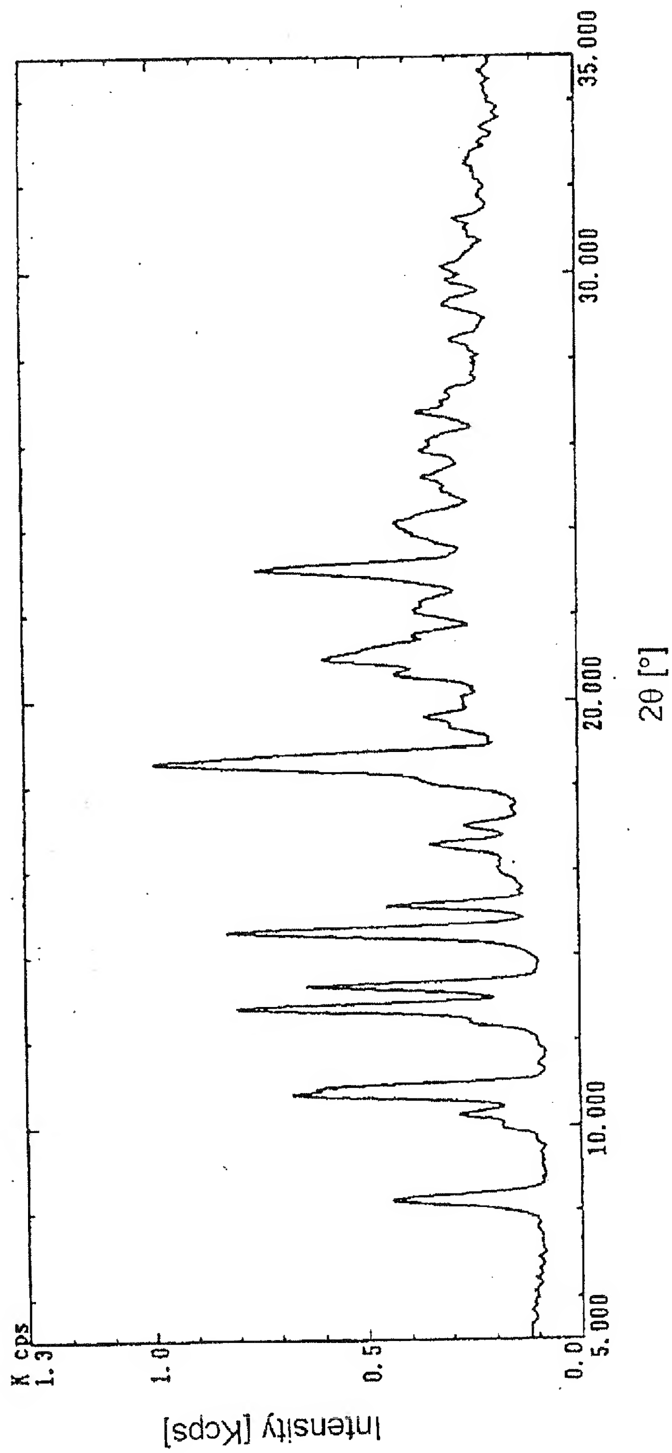

K cps
1.3
1.0
0.5
0.0
5.000
10.000
20.000
30.000
35.000
2θ [°]
Intensity [Kcps]

Fig. 3

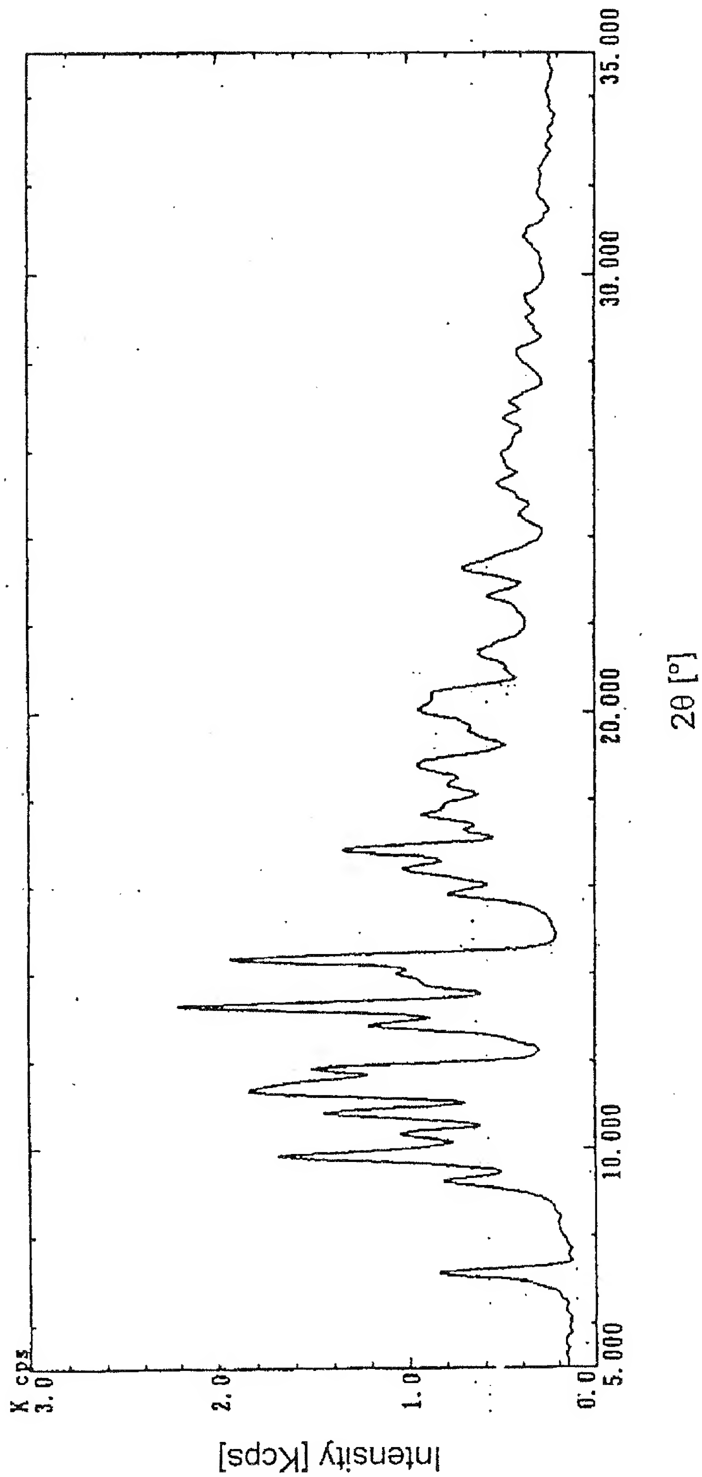

X cps
3.0
2.0
1.0
0.0
Intensity [Kcps]
5.000
10.000
20.000
30.000
35.000
2θ [°]

Fig. 4

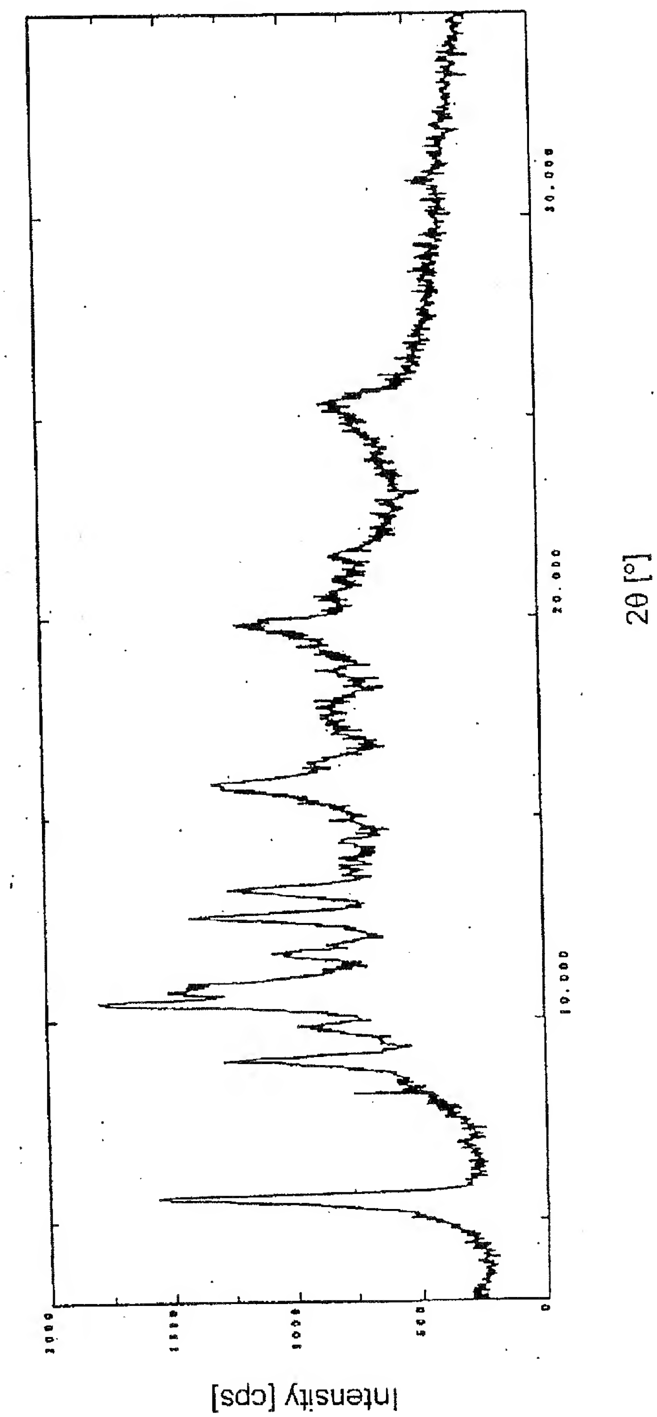
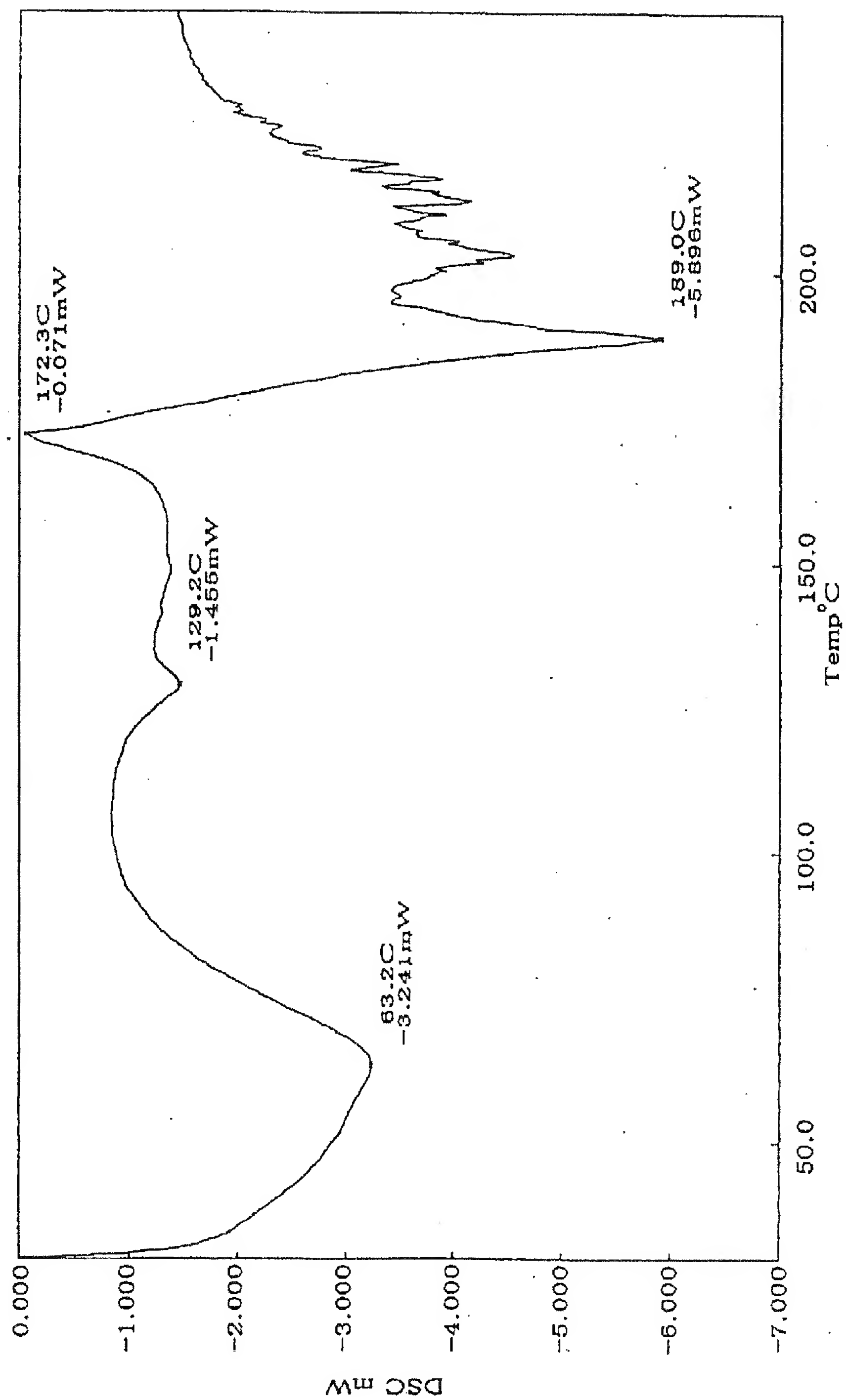


Fig. 5


172.3C
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129.2C
−1.455mW
63.2C
−3.241mW
189.0C
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0.000
−1.000
−2.000
−3.000
−4.000
−5.000
−6.000
−7.000
DSC mW
50.0
100.0
150.0
200.0
Temp°C

ERYTHROMYCIN DERIVATIVE HAVING NOVEL CRYSTAL STRUCTURES AND PROCESSES FOR THEIR PRODUCTION

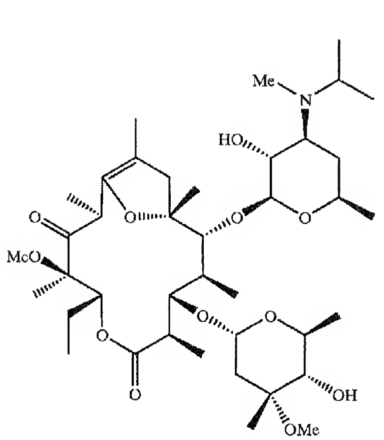
TECHNICAL FIELD

[0001] The present invention relates to novel crystals of fumarate salts of erythromycin derivatives and a method for their preparation.

BACKGROUND ART

[0002] The compound represented by formula (I):

(I)



[0003] is disclosed in, for example, JP 6-56873 A (WO93/24509) and JP 9-100291 A (WO97/06177). This compound is known to have the ability to enhance the movement of the digestive tract.

[0004] The preparation of this compound is disclosed in, for example, JP 9-100291 A, Bioorg. & Med. Chem. Lett. vol. 4(11), 1347 (1994) and JP 9-100291 A.

[0005] Conventionally, there are three patterns for crystals of a fumarate salt of compound (I): A-type crystal (hereinafter simply referred to as "A-type crystal"), C-type crystal (hereinafter simply referred to as "C-type crystal") and D-type crystal (hereinafter simply referred to as "D-type crystal"). Each of the A-type, C-type and D-type crystals is disclosed in JP 9-100291 A and can be prepared as described in this publication.

[0006] The A-type crystal may be prepared from a fumarate salt of compound (I) through recrystallization from a mixed solvent of methanol and isopropanol. The molar ratio between compound (I) and fumarate is 2:1. The A-type crystal provides the diffraction pattern as shown in **FIG. 1** when measured by X-ray diffractometry with Cu—Kα radiation.

[0007] The C-type crystal may be prepared from a fumarate salt of compound (I) through treatment with ethyl acetate. The molar ratio between compound (I) and fumarate is 1:1. The C-type crystal provides the diffraction pattern as shown in **FIG. 2** when measured by X-ray diffractometry with Cu—Kα radiation.

[0008] The D-type crystal may be prepared from a fumarate salt of compound (I) through treatment with a mixed solvent of ethyl acetate and water. The molar ratio between compound (I) and fumarate is 2:1. The D-type crystal provides the diffraction pattern as shown in **FIG. 3** when measured by X-ray diffractometry with Cu—Kα radiation.

[0009] Among the A-type, C-type and D-type crystals, the D-type crystal is reported to have high quality as a pharmaceutical and a starting material therefor because it is superior in stability or other properties to the other crystals (JP 9-100291 A).

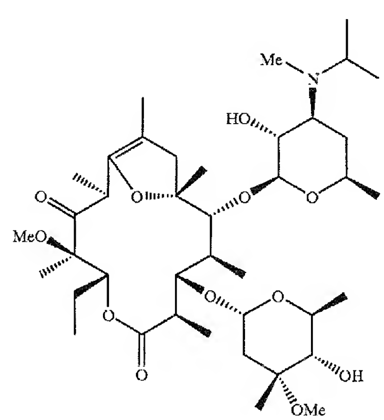
[0010] However, the prior art D-type crystal prepared by the conventionally known techniques as mentioned above which involve the following problems: a large volume of crystallization solvent remains in the crystal as a residual solvent; the residual solvent is difficult to remove during drying procedure; and the dryness of residual solvent cannot be below 1500 ppm. In this case, the residual solvent remaining in the D-type crystal is ethyl acetate, which is less toxic and less risky for human health (see "Guideline for residual solvents in pharmaceuticals" attached to the Notification No. 307 of Mar. 30, 1998 delivered from the director of Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare, Japan). However, it is naturally more desirable to reduce the content of such a less toxic solvent remaining in the crystal in a case where the crystal is intended to be used as a starting material for pharmaceuticals. Preferably, the content of residual solvent should be reduced to 1500 ppm or below, more preferably 1000 ppm or below. The prior art D-type crystal also involves another problem of having a small particle size, which often leads to tabletting troubles during the preparation of tablets comprising this crystal.

DISCLOSURE OF THE INVENTION

[0011] As a result of extensive and intensive efforts made to overcome the above problems in the prior art, the present inventors found structurally novel crystals of a fumarate salt of compound (I), which were different from known crystals, and finally completed the invention based on this finding.

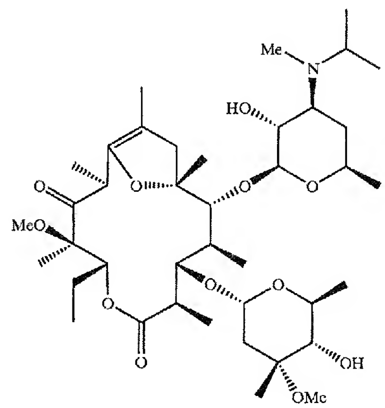
[0012] Namely, the present invention is directed to an E-type crystal of a fumarate salt of the compound represented by formula (I):

(I)



[0013] wherein said E-type crystal has strong X-ray diffraction peaks at diffraction angles (2θ) of 5.6° and 10.4° as measured by X-ray diffractometry with Cu—Kα radiation.

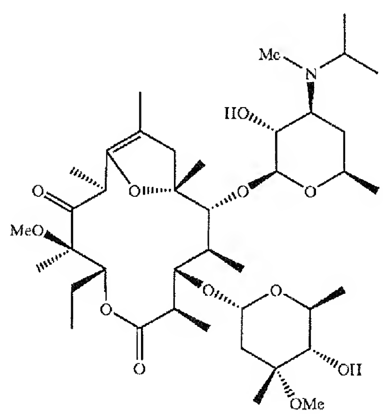
[0014] The present invention is also directed to a method for preparing an E-type crystal of a fumarate salt of the compound represented by formula (I):



(I)

[0015] which comprises treating a C-type crystal of a fumarate salt of compound (I) in a mixed solvent of ethyl acetate and water at 20° C. to 40° C., wherein said E-type crystal has strong X-ray diffraction peaks at diffraction angles (2θ) of 5.6° and 10.4° as measured by X-ray diffractometry with Cu—Kα radiation.

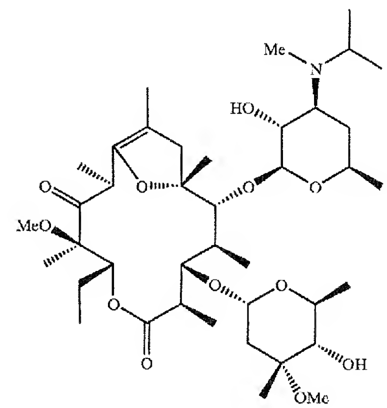
[0016] Further, the present invention is directed to a D-type crystal of a fumarate salt of the compound represented by formula (I):



(I)

[0017] which is obtainable via an E-type crystal of a fumarate salt of compound (I) having strong X-ray diffraction peaks at diffraction angles (2θ) of 5.6° and 10.4° as measured by X-ray diffractometry with Cu—Kα radiation.

[0018] Furthermore, the present invention is directed to a method for preparing a D-type crystal of a fumarate salt of the compound represented by formula (I):



(I)

[0019] which comprises obtaining the D-type crystal via an E-type crystal of a fumarate salt of compound (I) having strong X-ray diffraction peaks at diffraction angles (2θ) of 5.6° and 10.4° as measured by X-ray diffractometry with Cu—Kα radiation.

BRIEF DESCRIPTION OF DRAWINGS

[0020] **FIG. 1** shows a powder X-ray diffraction pattern of the A-form crystal.

[0021] **FIG. 2** shows a powder X-ray diffraction pattern of the C-form crystal.

[0022] **FIG. 3** shows a powder X-ray diffraction pattern of the D-form crystal.

[0023] **FIG. 4** shows a powder X-ray diffraction pattern of the E-form crystal.

[0024] **FIG. 5** shows a DSC spectrum of the E-form crystal.

BEST MODE FOR CARRYING OUT THE INVENTION

[0025] The structurally novel crystal of a fumarate salt of the erythromycin derivative represented by formula (I) according to the present invention (hereinafter simply referred to as "E-type crystal") provides the diffraction pattern as shown in **FIG. 4** when measured by X-ray diffractometry with Cu—Kα radiation. **FIG. 4** shows strong peaks at diffraction angles (2θ) of 5.6° and 10.4°.

[0026] These X-ray diffraction angles can be measured using various devices that are commercially available, such as a powder X-ray diffractometer. The details on the measurement principle of powder X-ray diffractometry can be found in the Japanese Pharmacopoeia, 13th Edition, published by Hirokawa Publishing Co. (1996) pp. B471-B475, the Japanese Pharmacopoeia, 14th Edition, published by Hirokawa Publishing Co. (2001) pp. B614-B619 and elsewhere. In general, the diffraction angle has an acceptable error of around ±0.2°.

[0027] As used herein, the term "dryness" refers to the content of residual solvent which reaches an almost unchanged level during drying procedure, more specifically refers to the content at a point where the drying procedure produces a less than 100 ppm/hr decrease in the content of residual solvent.

[0028] The present invention will be described below in more detail.

[0029] The method for preparing the E-type crystal according to the present invention can start with the C-type crystal.

[0030] The C-type crystal may be prepared by treating the A-type crystal with ethyl acetate, as described in JP 9-100241 A.

[0031] Further, the A-type crystal may be prepared by treating a fumarate salt of compound (I) with a mixed solvent of methanol and isopropanol, as described in JP 6-56873 A and JP 9-100241 A.

[0032] The E-type crystal of the present invention can be prepared by suspending the C-type crystal in a mixed solvent of ethyl acetate and water. The C-type crystal may be used either in isolated crystal or as a suspension in the solvent, but preferably used as a suspension in the solvent. In a preferred embodiment, the A-type crystal is treated with ethyl acetate to yield the C-type crystal as a suspension in ethyl acetate, which is further suspended by addition of water.

[0033] In the mixed solvent used in this suspension procedure, the mixing ratio between ethyl acetate and water is usually set to 99:1 to 95:5, preferably 97:3 to 95:5. The suspension procedure is usually performed at a temperature of 20° C. to 40° C., preferably 20° C. to 30° C. A temperature below 20° C. tends to stimulate the conversion into the D-type crystal. The suspension procedure is usually continued for 30 minutes to 300 minutes, preferably 60 minutes to 240 minutes.

[0034] The resulting E-type crystal may be separated from the solvent by filtration, centrifugation or the like. The separated E-type crystal may be dried under reduced pressure or other conditions, but preferably dried under reduced pressure. The drying temperature is usually 20° C. to 60° C., preferably 30° C. to 50° C.

[0035] The E-type crystal may be suspended in a mixed solvent of ethyl acetate and water at a temperature below 20° C. to yield the D-type crystal. In the mixed solvent used here, the mixing ratio between ethyl acetate and water is preferably set to 99:1 to 97:3. The suspension procedure is preferably performed at a temperature of −20° C. to 20° C. and usually continued for 1 hour to 12 hours, preferably 3 hours to 11 hours, more preferably 5 hours to 10 hours.

[0036] In order to prepare the D-type crystal with an average particle size sufficient to avoid tabletting troubles (preferably 90 μm or more, more preferably 100 μm or more) from the E-type crystal, the mixing ratio between ethyl acetate and water is preferably set to 98.1:1.9 to 97:3 in the mixed solvent used for crystallization. The suspension procedure is performed at a temperature of 10° C. to 20° C., preferably 11° C. to 19° C., more preferably 13° C. to 18° C. In order to stimulate the conversion into the D-type crystal or to improve the yield of the D-type crystal, the suspension may further be cooled to −20° C. to 10° C., preferably −15° C. to 10° C. The suspension procedure is usually continued for several minutes to 20 hours, preferably 5 minutes to 4 hours, more preferably 10 minutes to 2 hours. In a case where the suspension is further cooled, the suspension procedure is usually continued for additional several minutes to 20 hours, preferably around 1 hour.

[0037] It should be understood that the period of time required for the individual suspension procedures mentioned above refers to the minimum period of time required to prepare the E-type crystal, required to prepare the D-type crystal from the E-type crystal and required to prepare the D-type crystal with a large average particle size from the E-type crystal. The individual suspension procedures may be continued beyond the minimum period of time, depending on the degree of crystal growth or the convenience of preparation steps.

[0038] In preparing the D-type crystal via the E-type crystal, the D-type crystal can also be prepared continuously from the C-type crystal via the E-type crystal by merely controlling the temperature, without isolating the E-type crystal during preparation.

[0039] The resulting D-type crystal may be separated from the solvent by filtration, centrifugation or the like, and then dried under reduced pressure. The drying temperature is preferably 20° C. to 70° C. The D-type crystal of the present invention may completely (100%) or partially be composed of compound molecules prepared via the E-type crystal. In the latter case, the D-type crystal prepared via the E-type crystal may be contained at any percentage as long as the content of residual solvent does not exceed 1500 ppm, preferably not exceed 1000 ppm, and/or tabletting troubles do not occur.

[0040] The D-type crystal prepared via the E-type crystal in this way ensures a residual solvent content of 1500 ppm or below, which could not be achieved by the prior art D-type crystal. In addition, the D-type crystal thus prepared further ensures a residual solvent content of 1000 ppm or below and is also easier to dry than the prior art D-type crystal; it is therefore more preferable as an active pharmaceutical ingredient. The D-type crystal partially prepared via E-type crystal also ensures a residual solvent content of 1500 ppm or below, which could not be achieved by the prior art D-type crystal. This D-type crystal further ensures a residual solvent content of 1000 ppm or below and is also easier to dry than the prior art D-type crystal; it is also therefore more preferable as an active pharmaceutical ingredient.

[0041] Further, the D-type crystal with a large average particle size prepared under the conditions mentioned above cannot be obtained by the prior art techniques and allows avoidance of tabletting troubles; it is therefore particularly advantageous in preparing pharmaceuticals.

[0042] The content of residual solvent may be determined in a known manner, for example, by gas chromatography. The details on gas chromatography can be found in the Japanese Pharmacopoeia, 13th Edition, published by Hirokawa Publishing Co. (1996) pp. B83-B94, the Japanese Pharmacopoeia, 14th Edition, published by Hirokawa Publishing Co. (2001) pp. B98-B114 and elsewhere. In general, gas chromatography will cause a measurement error falling within around ±1%. The compound of the present invention can also be determined for its average particle size in a

known manner or using various devices that are commercially available, such as a dry particle size distribution analyzer. In general, such a particle size distribution analyzer will cause a measurement error falling within around ±5%.

EXAMPLES

[0043] The present invention will be further described in the following examples, which are provided for illustrative purposes only and are not intended to limit the scope of the invention.

[0044] In these examples and comparison examples, X-ray diffractometry was performed using a powder X-ray diffractometer RINT-1100 (Rigaku), the content of residual solvent was determined using a gas chromatograph GC-17A (Shimadzu Corp.), and the average particle size was determined using a particle size distribution analyzer RPS-95 (Seishin Enterprise Co., Ltd.). The content of residual solvent had a measurement error of around ±1%, while the average particle size had a measurement error of around ±4%.

Example 1

[0045] A fumarate salt of compound (I) (50.0 g) was dissolved in ethyl acetate (400 mL) and methanol (40 mL) at room temperature. The solution was then concentrated to dryness under reduced pressure at room temperature. The resulting dried product was stirred in ethyl acetate (415 mL) at 25° C. for 1 hour to give a suspension of a C-form crystal. Water (4.15 mL) was added to this suspension, followed by stirring at 25° C. for 0.5 hours. Water (4.15 mL) was further added and stirred at 25° C. for 0.5 hours. Water (4.15 mL) was further added and stirred at 25° C. for 0.5 hours. Water (4.15 mL) was further added and stirred at 25° C. for 0.5 hours. The suspension was then cooled to 20° C., stirred for 1 hour, and filtered to give a wet crystal (43.7 g). This wet crystal was dried under reduced pressure at 40° C. for 3 hours to give a crystal of the fumarate salt of compound (I) (34.1 g). This crystal was confirmed to be an E-form crystal having strong peaks at diffraction angles (2θ) of 5.60 and 10.40 as measured by X-ray diffractometry. **FIG. 5** shows a DSC spectrum of the resulting E-form crystal.

Example 2

[0046] A fumarate salt of compound (I) (20 g) was stirred in ethyl acetate (166 mL) at 25° C. for 2 hours to give a C-form crystal. After addition of water (2.4%, 4.0 mL), this C-form crystal was gradually cooled to ensure its complete conversion into E-form. The suspension was further cooled to 15° C. and stirred for 3 hours, followed by cooling to −10° C. The resulting crystal was then isolated to give a wet D-form crystal (20.4 g, average particle size: 302 μm). This wet D-form crystal was dried under reduced pressure at 25° C. for 1 hour and further dried at 60° C. to give the D-form crystal of the fumarate salt of compound (I). The resulting D-form crystal was found to have a residual solvent content of 78 ppm.

Example 3

[0047] Starting with a C-form crystal of a fumarate salt of compound (I), the same procedures as shown in Example 2 were repeated, except for adding 2.6% water, to give a D-form crystal with a particle size of 197 μm via an E-form crystal.

Example 4

[0048] A fumarate salt of compound (I) (11.6 kg) was dissolved at 25° C. in a mixed solvent of ethyl acetate (104.6 kg) and methanol (9.2 kg). After the solution was concentrated, ethyl acetate (86.8 kg) was added at 25° C. to the concentrated residue, followed by stirring at 24° C. for 1 hour to give a C-form crystal. After addition of water (2.0%, 1.9 kg), this C-form crystal was gradually cooled to ensure its conversion into E-form crystal. The suspension was further cooled to 15° C. and stirred for 1 hour, followed by cooling to −10° C. The resulting crystal was then centrifuged to give a wet D-form crystal (13.4 kg). This wet D-form crystal was dried under reduced pressure at 60° C. for 28 hours to give the D-form crystal of the fumarate salt of compound (I) (10.5 kg, yield 90.5%, average particle size: 141 μm). The resulting D-form crystal was found to have a residual solvent content of 988 ppm. In addition, no tabletting trouble was observed in this D-form crystal when used as a main component to prepare tablets.

Example 5

[0049] A fumarate salt of compound (I) (11.6 kg) was dissolved at 30° C. in a mixed solvent of ethyl acetate (94.2 kg) and methanol (9.1 kg). After the solution was concentrated, ethyl acetate (86.8 kg) was added at 22° C. to the concentrated residue, followed by stirring at 24° C. for 1 hour to give a C-form crystal. After addition of water (2.0%, 1.9 kg), this C-form crystal was gradually cooled to ensure its conversion into E-form crystal. The suspension was further cooled to 15° C. and stirred for 1 hour, followed by cooling to −10° C. The resulting crystal was then centrifuged to give a wet D-form crystal (13.2 kg). This wet D-form crystal was dried under reduced pressure at 60° C. for 10 hours to give the D-form crystal of the fumarate salt of compound (I) (10.5 kg, yield 90.5%, average particle size: 197 μm). The resulting D-form crystal was found to have a residual solvent content of 845 ppm. In addition, no tabletting trouble was observed in this D-form crystal when used as a main component to prepare tablets.

[0050] C-form crystals of a fumarate salt of compound (I) were similarly treated in accordance with Example 4 or 5 to give D-form crystals via E-form crystals (Examples 6 to 8).

Comparison Example 1

[0051] A fumarate salt of compound (I) (10.8 kg) was dissolved at 25° C. in a mixed solvent of ethyl acetate (87.6 kg) and methanol (8.5 kg). After the solution was concentrated, ethyl acetate (80.8 kg) was added at 25° C. to the concentrated residue, followed by stirring at 25° C. for 1 hour to give a C-form crystal. After addition of water (1.5%, 1.3 kg), this C-form crystal was cooled to 15° C. and stirred for 1 hour to ensure its conversion into D-form crystal. The suspension was further cooled to −10° C. and stirred for 1 hour. The resulting crystal was then centrifuged to give a wet D-form crystal (12.7 kg). This wet D-form crystal was dried under reduced pressure at 60° C. for 16 hours to give the D-form crystal of the fumarate salt of compound (I) (10.8 kg, yield 87.4%, average particle size: 82 μm). Tabletting troubles were observed in this D-form crystal when used as a main component to prepare tablets.

[0052] A C-form crystal of a fumarate salt of compound (I) was similarly treated in accordance with Comparison

Example 1 to give a D-form crystal without going via an E-form crystal (Comparison Example 2).

[0053] Table 1 summarizes the properties of the D-type crystals prepared via E-type crystals (Examples 2 to 8) and the prior art D-type crystals (Comparison Examples 1 and 2).

TABLE 1

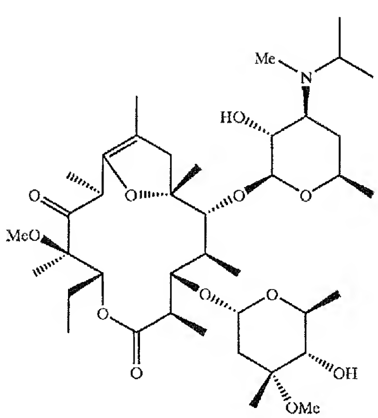
	Percentage of water (%)	Prepared via E-type crystal	Conditions for conversion of E-type crystal into D-type crystal	Drying conditions	Content of residual solvent (ppm)	Particle size (μm)	Tabletting trouble
Example 2	2.4	Completely	15° C., 3 hr → −10° C.	Reduced pressure 60° C., 8 hr	78	302	—
Example 3	2.6	Completely	15° C., 6 hr → −10° C.	Reduced pressure 60° C., 8 hr	—	197	—
Example 4	2.0	Partially	15° C., 1 hr → −10° C.	Reduced pressure 60° C., 28 hr	988	141	No
Example 5	2.0	Partially	15° C., 1 hr → −10° C.	Reduced pressure 60° C., 10 hr	845	197	No
Example 6	2.0	Partially	13° C., 0.5 hr → −10° C.	Reduced pressure 60° C., 9 hr	1049	—	—
Example 7	2.0	Partially	15° C., 1 hr → −10° C.	Reduced pressure 60° C., 6 hr	647	163	No
Example 8	2.0	Partially	15° C., 1 hr → −10° C.	Reduced pressure 60° C., 10 hr	893	185	No
Comparison Example 1	1.5	Not	—	Reduced pressure 60° C., 16 hr	2228	82	Yes
Comparison Example 2	1.5	Not	—	Aeration 45° C., 20 hr	1610	61	Yes

INDUSTRIAL APPLICABILITY

[0054] The E-form crystal of a fumarate salt of compound (I) according to the present invention enables the preparation of the D-form crystal with superior properties including a reduced content of residual solvent and high suitability for formulation. More specifically, the E-form crystal is characterized by (1) providing pharmaceuticals with superior quality and (2) allowing the efficient preparation of pharmaceuticals; it is therefore extremely useful in pharmaceutical preparation.

1. An E-type crystal of a fumarate salt of the compound represented by formula (I):

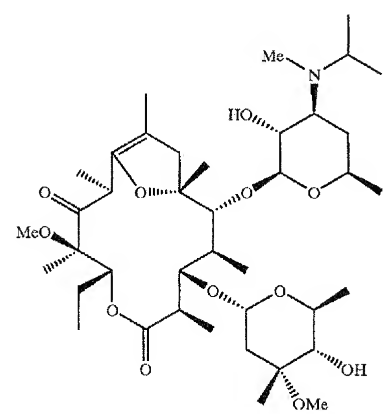
(I)



wherein said e-type crystal has strong x-ray diffraction peaks at diffraction angles (2θ) of 5.6° and 10.4° as measured by x-ray diffractometry with Cu—Kα radiation.

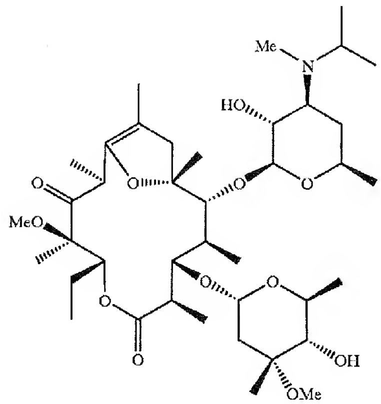
2. A method for preparing an E-type crystal of a fumarate salt of the compound represented by formula (I):

(I)



which comprises treating a C-type crystal of a fumarate salt of compound (I) in a mixed solvent of ethyl acetate and water at 20° C. to 40° C., wherein said E-type crystal has strong X-ray diffraction peaks at diffraction angles (2θ) of 5.6° and 10.4° as measured by X-ray diffractometry with Cu—Kα radiation.

3. A D-type crystal of a fumarate salt of the compound represented by formula (I):



(I)

which is obtainable via an E-type crystal of a fumarate salt of compound (I) having strong X-ray diffraction peaks at diffraction angles (2θ) of 5.6° and 10.4° as measured by X-ray diffractometry with Cu—Kα radiation.

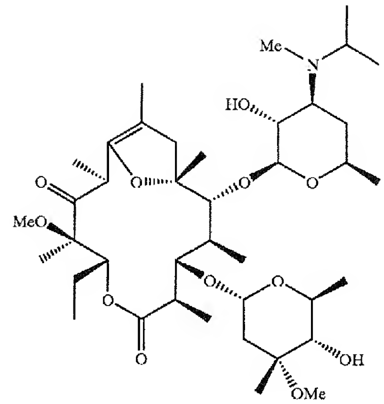
4. The D-type crystal according to claim 3, wherein the crystal has a residual solvent content of 1500 ppm or below.

5. The D-type crystal according to claim 3, wherein the crystal has a residual solvent content of 1000 ppm or below.

6. The compound according to any one of claims 3 to 5, wherein the crystal has an average particle size of 90 μm or more.

7. The compound according to any one of claims 3 to 5, wherein the crystal has an average particle size of 100 μm or more.

8. A method for preparing a D-type crystal of a fumarate salt of the compound represented by formula (I):



(I)

which comprises obtaining the D-type crystal via an E-type crystal of a fumarate salt of compound (I) having strong X-ray diffraction peaks at diffraction angles (2θ) of 5.6° and 10.4° as measured by X-ray diffractometry with Cu—Kα radiation.

9. The method according to claim 8, wherein the D-type crystal of a fumarate salt of compound (I) has a residual solvent content of 1500 ppm or below.

10. The method according to claim 8, wherein the D-type crystal of a fumarate salt of compound (I) has a residual solvent content of 1000 ppm or below.

11. The method according to any one of claims 8 to 10, wherein the D-type crystal of a fumarate salt of compound (I) has an average particle size of 90 μm or more.

12. The method according to any one of claims 8 to 10, wherein the D-type crystal of a fumarate salt of compound (I) has an average particle size of 100 μm or more.

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